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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,129	12/06/2001	Bryan M. O' Hara	0100-001US	4772

7590 06/01/2004

Eugene Moroz
Morgan & Finnegan, L L P
345 Park Avenue
New York, NY 10154

EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,129	O' HARA, BRYAN M.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-100* is/are pending in the application.

4a) Of the above claim(s) *14-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/30/03, 9/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I (Claims 1-13 and 100) in the paper filed March 3,2004 is acknowledged.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, papers filed January 30, 2003 and September 25, 2003, are attached to the instant Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically in claim 1 part c, there is a reference to a third plasmid, it is not clear if in this case the third plasmid is additionally inserted into the yeast construct of part-a or if the

construct of part-a and part-c each comprise only two plasmids thereby representing two separate yeasts used for the testing of an unknown compound were the results are compared between the yeast of part-a and part-c. Clarification is required.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant invention is drawn to a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase. The method comprises contacting a yeast cell comprising two plasmids containing fusion proteins with p51 and p66 and a reporter gene that is activated in the presence of the fusion complex. The method includes comparing the level of activity between the reporter gene activity in the presence and the absence of a test compound. The method also comprises a yeast cell in which the p66 plasmid contains a mutation associated with resistance of HIV-1 to at least one NNRTI. The invention of claim 100 is drawn to a pharmaceutical, a composition, resulting from the final method step.

The specification shows a method of screening compounds for complex formation in the absence or presence of a test compound.

The claims encompass a genus of compounds defined only by their function [enhancing complex formation] wherein the relationship between the structural features of members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Although the description does not provide working examples of the pharmaceutical compound, the description teaches a method for The instant invention is drawn to a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase, and the person skilled in the art can understand how to use the screening method considering the common general knowledge.

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention Edith

all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the use of drawings or structural chemical formulas that show that the invention was complete, or describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

The claimed invention is drawn to a pharmaceutical formulation identified by the method of claim 1. However, no structural or specific functional characteristics of such a pharmaceutical formulation is provided, nor is there any indication that the artisan actually implemented the method of claim 1 so as to identify any pharmaceuticals with which to employ the method of making the pharmaceutical formulation. This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant invention is drawn to a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase. The method comprises contacting a yeast cell comprising two plasmids containing fusion proteins with p51 and p66 and a reporter gene that is activated in the presence of the fusion complex. The method includes comparing the level

of activity between the reporter gene activity in the presence and the absence of a test compound. The method also comprises a yeast cell in which the p66 plasmid contains a mutation associated with resistance of HIV-1 to at least one NNRTI. The invention of claim 100 is drawn to a pharmaceutical, a composition, resulting from the final method step.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The specification shows a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase.

Claim meets the utility requirement of 35 U.S.C. § 101. Only one specific, substantial, and credible utility is required to support the requirements of 35 U.S.C. § 101. In the instant case the presence or absence of the complex between p66 and p51 is useful in diagnostic methods relating to the resistance to non-nucleoside reverse transcriptase inhibitors.

The instant fact pattern fails to disclose any particular structure for the claimed pharmaceutical formulation. The specification does not provide any guidance or any working

examples in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed pharmaceutical formulation without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C. § 112 first paragraph.

Therefore, the instant invention is not enabled for the method of making a pharmaceutical composition using the screening method of claim 1.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 11 and 13 rejected under 35 U.S.C. 102(a) as being anticipated by Tachedjian et al. (Proceeding of the National Academy of Science, June 19, 2001).

The instant invention is drawn to a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase (RT). The method comprises contacting a yeast cell comprising two plasmids containing fusion proteins with p51 and p66 and a reporter gene that is activated in the presence of the fusion complex. The method includes

comparing the level of activity between the reporter gene activity in the presence and the absence of a test compound. The method also comprises a yeast cell in which the p66 plasmid contains a mutation associated with resistance of HIV-1 to at least one NNRTI. Claims 2-8 indicate the specifics regarding the level of NNRTI resistance of HIV-1 reverse transcriptase and claims 10-13 indicate specific point mutations. An additional aspect of the invention is a method of making a pharmaceutical; the claim is technically drawn to the composition as the final method step results in the composition.

Tachedjian et al. disclose a yeast 2 hybrid (Y2H) assay in which a yeast comprising a wild type p66 and p51 plasmid are inserted into a CYT10-5d yeast comprising the integrated Gal1-lacZ gene with the lexA operator which is the reporter construct. The wild type p66 and p51 subunits are compared to the mutant Y181C p66 subunit, in the presence of a compound, nevirapine (see figure 2 and page 7190, column 1). Each p66 subunit, mutant and normal, is compared to the activity in the absence of the compound. The reference discloses that novel allosteric inhibitors may be selected by using this assay (Page 7193, last paragraph). Therefore, the instant invention is anticipated by Tachedjian et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tachedjian et al. ("Tach-1" Proceedings of the National Academy of Science, June 2000) and Tachedjian et al. ("Tach-2"Proceeding of the National Academy of Science, June 19, 2001) in view of Bacheler et al. (Journal of Virology June 2001).

The instant invention is drawn to a method of measuring complex formation between wild type subunit p66 and p51 of HIV-1 reverse transcriptase (RT). The method comprises contacting a yeast cell comprising two plasmids containing fusion proteins with p51 and p66 and a reporter gene that is activated in the presence of the fusion complex. The method includes comparing the level of activity between the reporter gene activity in the presence and the absence of a test compound. The method also comprises a yeast cell in which the p66 plasmid contains a mutation associated with resistance of HIV-1 to at least one NNRTI. Claims 2-8 indicate the specifics regarding the level of NNRTI resistance of HIV-1 reverse transcriptase and claims 10-13 indicate specific point mutations. An additional aspect of the invention is a method of

making a pharmaceutical; the claim is technically drawn to the composition as the final method step results in the composition.

Tachedjian et al. ("Tach-1") teach a method yeast 2 hybrid (Y2H) assay for RT dimerization, which can be used to screen for inhibitors that would prevent the process of dimerization (See page 6339, last paragraph). An assay that is able to measure the activity of dimerization in the presence or absence of a compound can detect the effect of the compound. An unknown compound can either have no effect regarding the dimerization of the subunits or the compound could either increase or decease the association of the complex between p66 and p51. The reference uses a yeast 2 hybrid (Y2H) assay using a *S. cerevisiae* strain CTY105-d which has the Gal1-lacZ gene with the lexA operator integrated (see material and methods; page 6334, column2, 3rd paragraph and table 2). The yeast have been transformed with a p66 and a p51 fusion constructs, meeting the claim requirements of having 2 plasmids expressing fusion proteins and a reporter gene which is activated in the presence of the complex. The reference also teaches a comparison between the wild type p66 and p51 heterodimer formation and comparing the result to various mutation in the p66 protein (see table 3, page 6338). The reference also discloses the Y2H assay to test the TSAO compound and determine if the compound affects the heterodimer formation (see page 6339, column 1, first paragraph). The reference does not teach using mutant sequences that are associated with resistance to at least one NNRTI in an assay determining the effect of a compound.

Tachedjian et al. ("Tach-2") teaches a Y2H assay in which a yeast comprising a wild type p66 and p51 plasmid are inserted into a CYT10-5d yeast comprising the integrated Gal1-lacZ gene with the lexA operator which is the reporter construct. The wild type p66 and p51 subunits

are compared to the mutant Y181C p66 subunit, in the presence of a compound, nevirapine (see figure 2 and page 7190, column 1). Each p66 subunit, mutant or normal, is compared to the activity in the absence of the compound. The reference teaches that novel allosteric inhibitors may be selected by using this assay (Page 7193, last paragraph). The reference does not teach p66 polypeptides having 5 mutations associated with an increase in the resistance to NNRTI.

Bacheler et al. teach that mutations in the RT gene correlate with the phenotypic resistance of HIV-1 replication to efavirenz (see table 1). A single amino acid substitution at position 103 in RT confers significant resistance to efavirenz , nevirapine and delavirdine, multiple mutations are also observed in patients receiving combination NNRTI therapy. The *in vitro* findings suggest that a number of resistance mutations that are commonly seen *in vivo* may confer clinically significant cross-resistance to all of the presently approved NNRTI's (see discussion, page 5006, column 1, 1st paragraph). The reference has also created HIV variants that are resistant to NNRTI using site directed mutagenesis (see table 3, page 5005). There is a great need for new drug candidates with unique resistance characteristics for use in NNRTI-based combination therapy.

It would have been obvious to one of ordinary skill in the art at the time the inventions was made to use a screening assay using a Y2H system for the purpose of determining the effect of an unknown compound on the heterodimer formation of p66 and p51 in a cell as taught by Tach-1. One having ordinary skill in the art would have had a high expectation of success in assessing the effect of a NNRTI on the ability of an RT mutant to be able to from a heterodimer as taught in Tach-2. It would have been obvious from the art and from Bacheler et al. that mutations in RT lead to the reduced effect of the NNRTI inhibitors in patients receiving

combination NNRTI therapy. Bacheler et al. sets out that there is a need to determine effective inhibitors in patient populations that have develop some resistance already. The reference teaches various mutations observed in the HIV-1 RT region in patients receiving this type of therapy and the reference also has specifically introduced these same mutation into HIV to see if the drug resistant phenotype is observed after making the specific mutations. It was observed that samples from patients who are resistance to NNRTI have multiple mutations (up to six) mutations in the RT gene. It would have been obvious to one of ordinary skill in the art to introduce specific mutations into the RT gene which emulate those mutations seen to arise in patient population being treated with standard NNRTI therapy. The screening assay is to produce new drugs that can be effective in patients that have developed a resistance to the conventional drugs. There is a high expectation of success in applying these techniques of Tach-1 and Tach-2 using the mutations as set out in Bacheler et al. because the reference already established that the site directed mutagenesis in the RT gene resulted in the resistance to efavirenz , nevirapine and delavirdine.

Therefore, the instant inventions is obvious over Tachedjian et al. ("Tach-1" Proceedings of the National Academy of Science, June 2000) and Tachedjian et al. ("Tach-2"Proceeding of the National Academy of Science, June 19, 2001) in view of Bacheler et al. (Journal of Virology June 2001).

Conclusion

No claims allowed.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PATENT EXAMINER 5/28/04